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<p>(21) International Application Number: PCT/US97/15312</p> <p>(22) International Filing Date: 5 September 1997 (05.09.97)</p> <p>(30) Priority Data: 60/025,599 6 September 1996 (06.09.96) US 9618687.9 6 September 1996 (06.09.96) GB</p> <p>(60) Parent Application or Grant (63) Related by Continuation US Not furnished (CIP) Filed on Not furnished</p> <p>(71) Applicant (for all designated States except US): BIOCHEM PHARMA, INC. [CA/CA]; 275 Armand Frappier Boulevard, Laval, Quebec H7V 4A7 (CA).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ST-DENIS, Yves [CA/CA]; 3727 St-Hubert, Montreal, Quebec H7L 3Z9 (CA). SIDDIQUI, M., Arshad [CA/CA]; 117-2700 Thimons Boulevard, St-Laurent, Quebec H4R 2C4 (CA). CODY, Wayne, Livingston [US/US]; 1314 Maplewood Drive, Saline, MI 48176 (US). EDMUNDS, Jeremy, John [GB/US]; 3957 Beech Drive, Ypsilanti, MI 48197 (US).</p>	<p>PLUMMER, Janet, Samartino [US/US]; 8100 Huron River Drive, Dexter, MI 48130 (US).</p> <p>(74) Agent: MURRAY, Robert, B.; Nikaido, Marmelstein, Murray & Oram LLP, Suite 330, Metropolitan Square - "G" Street Lobby, 655 15th Street, N.W., Washington, DC 20005-5701 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
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(54) Title: LACTAM INHIBITORS OF THROMBIN

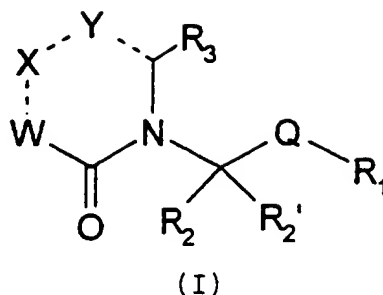
(57) Abstract

This invention relates to heterocyclic inhibitors of the enzyme thrombin, their preparation, and pharmaceutical compositions thereof having general formula (I), wherein W, X, Y R₁ to R₃ are as defined herein. Also, the invention relates to the use of such compounds and compositions as anticoagulants and as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction.

(I)

WE CLAIM:

1. A compound of formula (I):



wherein:

W and X are independently selected from CH-R₄, C-R₄, N-R₄,

N, O, S, SO and SO₂, provided that at least one of W and

10 X is selected from N-R₄, N, O, S, SO and SO₂;

Y is selected from CH-R₄, C-R₄ and C=O;

Q is selected from carbonyl, C=S and CH-R₄;

R₁ is a polar amino acid residue or derivative or analogue thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R₂ and R₂' are independently selected from H, halogen, C₁₋₁₆ alkyl optionally substituted with C₆₋₁₆ aryl, heterocycle or a C₃₋₇ cycloalkyl group; and

R₃ and R₄ are independently selected from H; NR₅R₆;

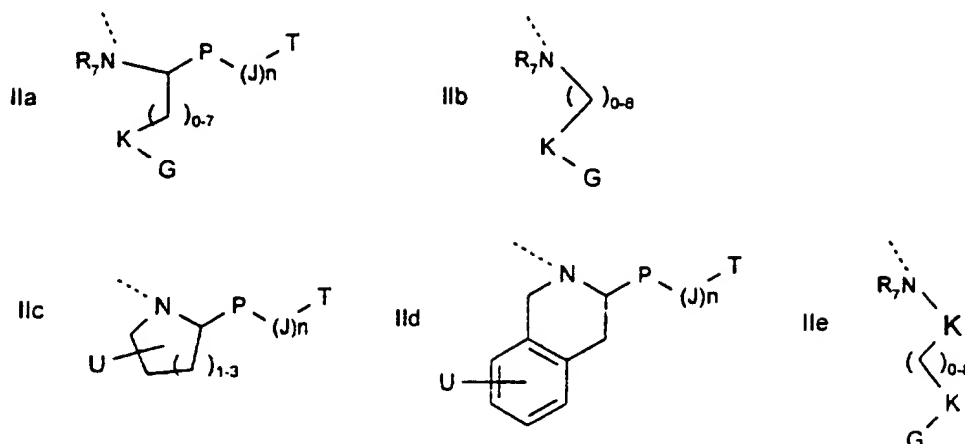
20 carboxyl; C₆₋₁₆ aryl or C₃₋₇ cycloalkyl optionally substituted with C₁₋₆ alkyl; C₁₋₁₆ alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR₅R₆ or a C₆₋₁₆ aryl, heterocycle or C₃₋₇ cycloalkyl group optionally substituted with halogen, hydroxyl, carboxyl, C₁₋₆ alkyl; an amino acid side chain; and a hydrophobic group; or

when Y is CH-R₄ or C-R₄ then R₃ and R₄ together with Y form a 5 or 6 member saturated or unsaturated carbocyclic ring;

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R₅ and R₆ are independently selected from H and C₁₋₄ alkyl.

2. A compound according to claim 1, wherein R_1 is one of formula IIa to IIe:



wherein:

R_7 is hydrogen or C_{1-6} alkyl;

K is a bond or $-NR_7-$;

G is C_{1-4} alkoxy; cyano; $-NHR_8$; $-CH_2-NHR_8$; $-C(NH)-NHR_8$;

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$-NH-C(NH)-NHR_8$; $-CH_2-NH-C(NH)-NHR_8$; a C_{6-12} cycloalkyl or aryl substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$, $-CH_2-NH-C(NH)-NHR_8$, halogen

C_{1-4} alkyl, aryl or heterocycle; or a 5 or 6 member, saturated or unsaturated heterocycle or heterobicycle optionally substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NH_2$, $-CH_2-NH-C(NH)-NHR_8$, halogen C_{1-4} alkyl, aryl or heterocycle; provided that G

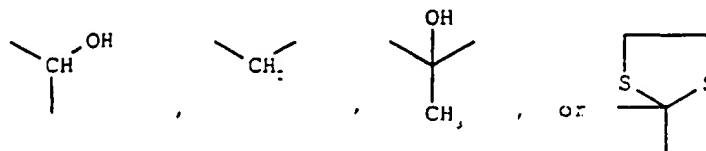
is other than unsubstituted indole and when G is C_{6-12} cycloalkyl or aryl then G is substituted with at least one group selected from $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$ or $-CH_2-NH-C(NH)-NHR_8$;

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U is cyano, $-NHR_8$, $-C(NH)-NHR_8$ or $-NH-C(NH)-NHR_8$;

R_8 is H, OH or NH_2 ;

P is a bond, $-C(O)-$, $-C(S)-$ or a bivalent group:



J is C_{1-6} alkylene optionally substituted with OH, NH_2 and

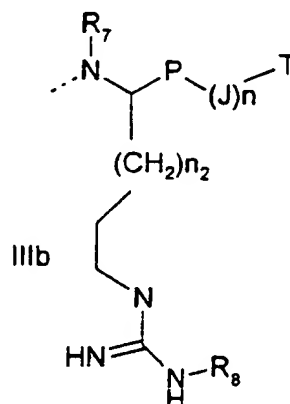
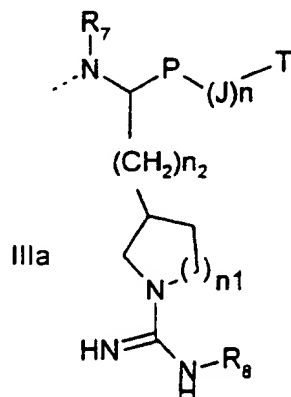
C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, O- R_4 , carboxyl, amino, a peptide chain, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted;

provided that R_1 is other than $-NHNH_2$.

3. A compound according to claim 2, wherein R_1 is selected from:

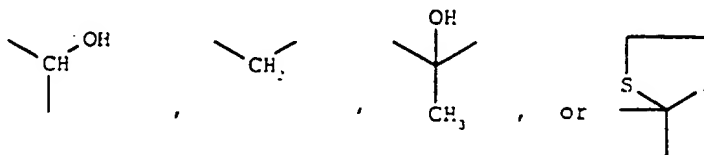


wherein:

R_7 is hydrogen or C_{1-6} alkyl;

R_8 is H, OH or NH_2

P is a bond, $-C(O)-$, $-C(S)-$ or a bivalent group:

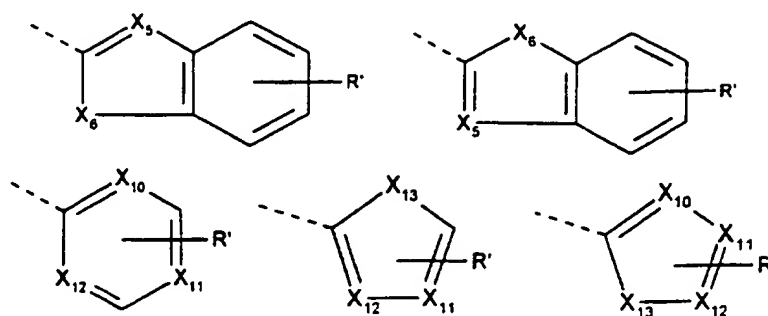


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, O- R_4 , carboxyl, amino, a peptide chain, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted.

4. A compound according to claim 3, wherein P is C(O), n is 0 and T is a heterocycle selected from the group consisting of:



wherein

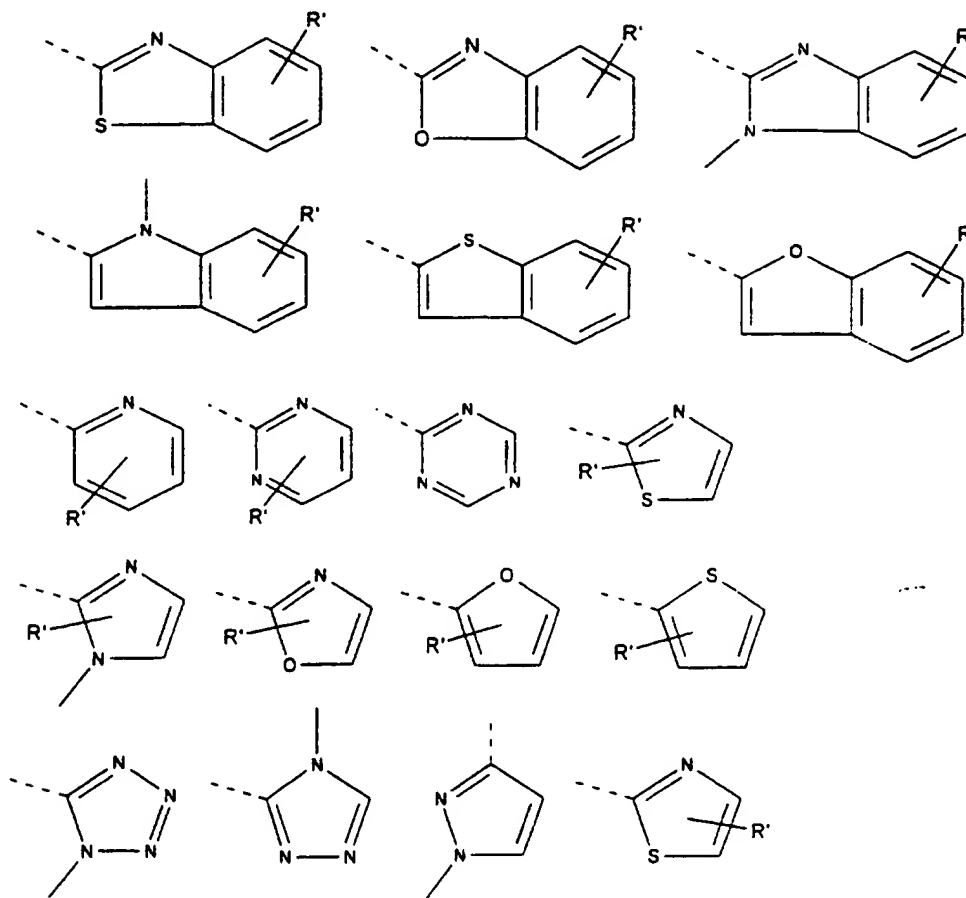
X_5 , X_{10} , X_{11} and X_{12} are each independently selected from the group consisting of N, or C- X_7 , where X_7 is hydrogen, C_{1-4} alkyl, or C_{5-8} aryl;

- 10 X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N- X_7 , or CH- X_7 ; and R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-16}$ alkyl-CO₂- C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

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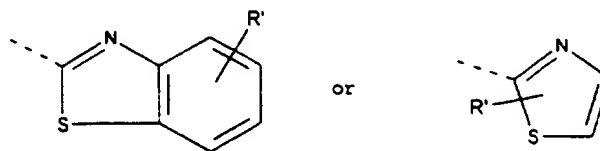
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5. A compound according to claim 4, wherein T is selected from the group consisting of:



wherein R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋₇ cycloalkyl, aryl or an aromatic heterocycle.

- 10 6. A compound according to claim 5, wherein T is selected from:



wherein R' is hydrogen, C₁₋₁₆ alkyl optionally carboxyl substituted, carboxyl, -C₀₋₁₆ alkyl-CO₂-C₁₋₁₆ alkyl, C₆₋₂₀ aralkyl, C₃₋₇ cycloalkyl, aryl or an aromatic heterocycle.

7. A compound according to claim 1, wherein one of W and X is N-R₄; and
R₄ is a hydrophobic group selected from C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl or C₂₋₂₀ alkynyl optionally interrupted by a carbonyl group, C₆₋₁₆ aryl, C₃₋₇ cycloalkyl, C₆₋₂₀ aralkyl, C₆₋₂₀ cycloalkyl substituted C₁₋₂₀ alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group and the ring portion is optionally substituted with C₁₋₆ alkyl; and a hydrophobic amino acid side chain.
- 10 8. A compound according to claim 7, wherein one of W and X is CH₂.
9. A compound according to claim 8, wherein W is CH₂; X is N-R₄ and Y is C=O or CH₂.
10. A compound according to claim 1, wherein R₂ and R₂' are both H.
- 20 11. A compound according to claim 1, wherein Q is C=O.
12. A compound according to claim 1, wherein Y is CH-R₄ or C-R₄ and R₃ and R₄ together with Y form a 5 or 6 member saturated or unsaturated carbocyclic ring.
13. A compound according to claim 12, wherein said carbocyclic ring is a phenyl ring.
14. A compound according to claim 1, selected from:
- 30 (1) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide;
- (2) N-[1-(benzothiazole-2 carbonyl)-4-guanidino-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide;
- (3) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide; (4) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-

piperazin-1-yl) acetamide;

- (5) N-[1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-{4-[(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-acetamide;
- (6) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl)-acetamide;
- (7) N-[1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl)-acetamide;
- (8) N-[1-(3-carbamimidoyl-benzyl)-2-oxo-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-acetamide;
- (9) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (10) 2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]acetamide;
- (11) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl]-acetamide;
- (12) N-[1-(4-aminocyclohexyl)-2-thiazol-2-ylethyl]-2-(2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-acetamide;
- (13) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-acetamide;
- (14) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-{2-benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-acetamide;
- (15) 2-{2-benzyl-4-[3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]-acetamide;
- (16) 2-(4-benzenesulfonyl-2-oxo-piperazin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide;
- (20) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-

acetamide;

- (21) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (22) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isopropyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (23) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isobutyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (24) 2-[2-sec-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;
- (25) 2-[2-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (26) 2-[2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (27) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-4-(3-phenyl-propyl)-2-pyridin-3-ylmethyl-piperazin-1-yl]-acetamide;
- (28) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (29) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[3-(4-chloro-benzyl)-2,5-dioxo-1-(3-phenyl-propyl)-piperidin-4-yl]-acetamide;
- (30) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (31) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-cyclohexylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (32) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-

thiazol-2-yl-ethyl]-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(33) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(34) N-[2-Benzothiazol-2-yl-1-(3-carbamimidoyl-benzyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(35) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methoxy-N-methyl-propionamide;

(36) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(37) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-2-phenethyl-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(38) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(39) N-(1-Formyl-4-guanidino-butyl)-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(40) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-chloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;

(41) N-[2-Benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(42) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-acetamide;

(43) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methyl-propionamide;

(44) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-

- piperazin-1-yl]-acetylamino)-3-(1-carbamimidoyl-piperidin-3-yl)-N-cyclopentyl-propionamide;
- (45) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(hydroxythiazol-2-yl-methyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (46) 2-(2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- 10 (47) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (48) 2-(2-Benzyl-3,6-dioxo-4-phenethyl-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (49) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- 20 (50) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- (51) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-hydroxymethyl-ethyl]-acetamide;
- (52) N-[1-(1-Carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- (53) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-1-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- 30 (54) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (55) 2-(2-Benzyl-4-[3-(4-methoxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-

piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

- (56) 2-[2-Benzyl-3,6-dioxo-4-(3-p-tolyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (57) 2-[2-Benzyl-4-[3-(4-chloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- 10 (58) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;
- (59) N-[1-Benzoyl-2-(1-carbamimidoyl-piperidin-3-yl)-ethyl]-2-(2-benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- (60) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-phenyl-ethyl]-acetamide;
- (61) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;
- 20 (62) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;
- (63) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;
- (64) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;
- 30 (65) 2-[2-Benzyl-4-[3-(4-nitro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (66) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

- (67) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;
- (68) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-methoxy-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;
- (69) 2-(4-Benzyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- 10 (70) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (71) 2-{2-Benzyl-4-[3-(4-isopropyl-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (72) 2-{2-Benzyl-4-[3-(4-hydroxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- 20 (73) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (74) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;
- (75) N-[4-(N-Methyl-guanidino)-1-(thiazole-2-carbonyl)-butyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;
- 30 (76) 2-[4-Butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (77) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-carbonyl)-ethyl]-acetamide;
- (78) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-

- carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (79) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(4-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (80) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- 10 (81) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2,5-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (82) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidine-1-(thiazole-2-carbonyl)-butyl]-acetamide;
- (83) N-[2-benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (84) N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- 20 (85) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (86) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(3-carbamimidoyl-phenyl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;
- (87) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- 30 (88) 2[4-butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]acetamide;
- (89) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (90) 2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-

- oxo-2-thiazol-2-yl-ethyl]-acetamide;
- (91) 2-[2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]acetyl-amino]-3-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;
- (92) 2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;
- (93) 3-(1-carbamimidoyl-piperidine-3-yl)-2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetyl-amino]-N-methyl-propionamide;
- (94) (3S)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[4-[3-(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl]-acetamide;
- (95) 2-(4-Benzenesulfonyl-2-oxo-piperazin-1-yl)-N-[1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-acetamide;
- (96) 4-[2-Carboxy-2-oxo-1-[2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-acetyl-amino]-ethyl]-cyclohexylamine;
- (97) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-piperazin-1-yl)-acetamide; (98) 5-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]pentylamine; (99) 4-(2S)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazan-1-ylmethyl-carboxamido]butylamine;
- (100) 4-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]guanidinobutane;
- (101) N-(4-carbamimidoyl-phenyl)-2-[2-cyclohexa-2,4-dienylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]acetamide;
- (102) N-(4-amino-cyclohexyl-methyl)-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;
- (103) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-(1-carboximidoyl-piperidin-4-ylmethyl)-acetamide;
- (104) N-(4-Amino-cyclohexyl-methyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide; and
- (105) N-(4-Carbamidoyl-benzyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide;

- (106) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide
- (107) 2-[4-Benzyl-2-[(diphenyl-methanesulfonylamino)-methyl]-3,6-dioxo-piperazin-1-yl]-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide;
- (108) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide;
- (109) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-(4-carbamimidoyl-2-chloro-benzyl)-acetamide;
- (110) N-(6-Amino-2-chloro-pyridin-3-ylmethyl)-2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetamide; and
- (111) {[4-((2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetyl-amino)-methyl)-2,5-dichloro-phenyl]-imino-methyl}-carbamic acid ethyl ester.

15. A compound according to claim 12, selected from:

- (17) 2-(4-benzoyl-2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide;
- (18) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-3,4-dihydro-2H-quinoxalin-1-yl]-acetamide; and
- (19) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2H-quinoxalin-1-yl)acetamide
- (112) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-acetamide;
- (113) N-(4-Guanidino-butyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2H-quinoxalin-1-yl)-acetamide; and
- (114) N-(1-Carbamidimidoyl-piperidin-4-ylmethyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2H-quinoxalin-1-

yl)-acetamide.

16. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.
17. A method according to claim 16, wherein said thrombotic disorder is venous thrombosis.
- 10 18. A method according to claim 16, wherein said thrombotic disorder is a pulmonary embolism.
19. A method according to claim 16, wherein said thrombotic disorder is arterial thrombosis.
20. A method according to claim 16, wherein said thrombotic disorder is myocardial infarction.
- 20 21. A method according to claim 16, wherein said thrombotic disorder is cerebral infarction.